marked up version of the paragraph of the specification , with the amendments indicated by underlining for additions, is attached hereto as Exhibit A. A "clean" copy of the specification paragraph, as amended, is attached hereto as Exhibit B.

Claims 1 and 22-26 will be pending upon entry of this Reply. Applicants note with appreciation that claims 1 and 22 are allowed. Claim 23 has been amended to more distinctly claim the subject matter which Applicants regard as their invention. The amendments are supported in the specification at page 4, lines 34 to 37 . No new matter is introduced. The above amendments do not represent acquiescence to the Examiner's rejections. Rather, they are made to expedite prosecution of the present application. Applicants emphasize for the record that the amendments are not narrowing in scope and reserve the right to pursue the subject matter of the original claims in a related application. In the interest of expediting prosecution, Applicants also have canceled claim 26 without prejudice and retain the right to pursue the subject matter of the canceled claim in a related application. The claim has not been canceled in response to any of the Examiner's rejections or objections. In sum, Applicants reserve the right to prosecute the subject matter of claim 26 or any other unclaimed subject matter, in one or more related applications. A marked up version of the amended claim indicating the changes is attached hereto as Exhibit C. For the Examiner's convenience, a copy of all pending claims is attached hereto as Exhibit D.

Sequence Compliance for Figure 1

The Examiner has indicated that the sequences in Figure 1 should be identified by SEQ ID numbers and comply with 37 CFR 1.821-1.825. Applicants respectfully submit that the above amendments to the specification have corrected the informalities; therefore the Examiner's objection has been obviated. Accordingly, Applicants request that the

replacement paragraph be entered into the specification by amendment and the objection be withdrawn.

The Rejection Under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn

The Examiner has maintained the rejection of claims 23-26 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In particular, the Examiner disagrees with Applicants' and alleges that the specification does not provide a representative number of species of the genus. The Examiner indicates that the claims are drawn to polypeptides having no limitations to the function of the polypeptides and concludes that the claims are drawn to a large variable genus of variants having MEK6 activity, unknown activity or no activity. The Examiner alleges that the specification does not describe the function of all the polypeptides derived or modified from SEQ ID NO:2 as encompassed in the claims.

Preliminarily, Applicants note that claim 26 has been canceled without prejudice thereby rendering the Examiner's rejection of that claim moot. In addition, Applicants submit that claim 23 has been amended to more distinctly and clearly claim that which the Applicants regard as the instant invention; however, Applicants address below the Examiner's rejection in order to avoid having such a rejection applied to claim 23 as amended.

Applicants remind the Examiner that the complete specific structure of each and every isolated DNA molecules encoding a polypeptide 90% identical to SEQ ID NO:2 need not be disclosed to satisfy the written description requirement. The legal standard for

written description purposes is met if the specification discloses relevant identifying structural and functional characteristics sufficient to show that Applicants were in possession of the claimed genus. As Applicants pointed out in the previously filed response, a number of species of the genus are provided by the specification, including the DNA molecules encoding polypeptides with an amino acid sequence of SEQ ID NO:2 or constitutively active variants with an amino acid substitution at the Serine at residue 207 or the Threonine at residue 211 with negatively charged amino acids such as glutamic acid or aspartic acid and constitutively inactive variants with an amino acid substitution at the Lysine at residue 69 (specification at page 6, line 31 to page 7, line 11). Thus, the structural attributes and characteristics of the claimed genus are recognized by one skilled the art based on the disclosure of such representative species.

Applicants had also explained to the Examiner in the previously filed response, the structure of the genus is clearly premised on the teachings in the specification which provide a specific sequence, *i.e.* SEQ ID NO:2 which corresponds to the amino acid sequences encoding a MEK6 polypeptide or variant thereof. Based on the teachings of the specification with respect to variants, the claimed genus of proteins that are variants of SEQ ID NO: 2 having at least 90% structural identity with the disclosed species are clearly defined in the instant specification such that one skilled in the art would recognize from the disclosure that Applicants were in possession of the genus of proteins that are variants of SEQ ID NO:2 with modifications at no more than a 10% of the amino acid residues (specification page 4, line 34 to page 6, line 6).

Furthermore, the instant pending claims require that the genus must be capable of a specified activity *i.e.*, have the capability to phosphorylate a substrate. Based on the teachings of the specification with respect to variants, the claimed genus of proteins that must

be variants of SEQ ID NO: 2 does not have substantial variation since all of the claimed variants must have at least 90% structural identity with the disclosed species and must have the capability to phosphorylate a substrate (see specification page 6, line 31 to page 7, line 2). The procedures for making the variants of SEQ ID NO:2 are described in the specification (for example at specification page 6, lines 13-20) or known in the art and the assays for identifying all of the at least 90% identical variants of SEQ ID NO:2 which are capable of the specified activity, *e.g.,* capable of phosphorylating a substrate are also described in the specification and known in the art (see specification at page 8, lines 17-28). Claims 24 and 25 dependent from claim 23 further relate to such variants with "not substantially diminished" ability to phosphorylate p38 and variants that are constitutively active, respectively. The specification also describes such variants and assays for identifying such variants (see specification page 6, lines 25 to 30 and page 6, line 31 to page 7, line 2, respectively). Accordingly, one skilled in the art would conclude that Applicants were in possession of the necessary common attributes possessed by members of the claimed genus.

In view of the foregoing, Applicants respectfully submit that the written description requirement has been met for pending claims 23-25 and that the rejection under 35 U.S.C. § 112, first paragraph should be withdrawn.

The Rejection Under 35 U.S.C. § 112, First Paragraph Should Be Withdrawn

The Examiner has maintained the rejection of claims 23-26 under 35 U.S.C. § 112, first paragraph, for lack of enablement. In particular, the Examiner alleges that the specification, while being enabling for the MEK6 of SEQ ID NO: 2, does not reasonably enable a MEK with structures different from SEQ ID NO: 2 because the specification allegedly does not provide sufficient enablement of a polypeptide of unknown function. The

Examiner explains that the function of a polypeptide can not be determined from its structure and the specification does not teach how to use polypeptides with unknown function. The Examiner indicates that claim 25 is drawn to variant polypeptides of SEQ ID NO:2 having "constitutively active" polypeptides and the specification does not teach how to use variant polypeptides of SEQ ID NO:2 having any activity. The Examiner concludes that the breadth of the claims is much larger than the scope enabled by the specification.

Again, Applicants note that claim 26 has been canceled without prejudice thereby rendering the Examiner's rejection of that claim moot. Claim 23 has been amended to more distinctly and clearly claim that which the Applicants regard as the instant invention and Applicants address below the Examiner's rejection in order to avoid having such a rejection applied to claim 23 as amended.

Applicants submit that under the legal test for enablement one skilled in the art could make and use the claimed invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 U.S.P.Q.2d 1217 (Fed. Cir. 1988). As discussed in the previous response, recombinant and mutagenesis techniques are known in the art and that it would be routine in the art to make the claimed polypeptide variants of MEK6. It would be routine to screen for variant sequences for a desired and specified activity. In fact, computer programs and algorithms and standard techniques are known in the art to be useful for selecting and predicting which residues to substitute, insert, delete and/or modify to permit identification of a limited number of structural variants that would be expected to have a desired utility/activity. One skilled in the art could reasonable predict the function of a particular polypeptide based on its structure, *i.e.*, based on what residues are altered and what residues are not altered within a particular

polypeptide. Moreover, Applicants re-direct the Examiner's attention to the specification which provides representative assays which can evaluate the effect of any modification made in MEK6. For example, page 6, line 31 to page 7, line 11 describe modifications made and methods for evaluating the effect of any modification on the polypeptide function or activity. In particular, Applicants direct the Examiner's attention to the specification at page 8, lines 18-28 of the specification.

Applicants submit that without references or reasonable scientific explanations with respect to why the specification and standard techniques known in the art would not be adequate for one skilled in the art to make and use the claimed invention without undue experimentation, the Examiner has not demonstrated his reasons for rejecting these claims. Applicants reiterate that guided by the specification and techniques known in the art, one skilled in the art could successfully make modified polypeptides and assay them for effect of such modifications using the representative assays provided in the specification or known in the art. Indeed, Applicants submit that not only does the specification provide sufficient guidance as to which modifications are likely to be successful for the desired activity, but also that the assays and methods for evaluating modifications of polypeptides, as encompassed by the instant claims, are known in the art and can be readily performed by the skilled artisan without undue experimentation.

In particular, Applicants submit that one skilled in the art would readily be able to determine whether a claimed polypeptide having a 90% identity with SEQ ID NO:2 would retain the claimed desired activity, *i.e.*, capability to phosphorylate a substrate, by using the representative methods and assays provided by the specification *e.g., see* page 8, line 17 to page 9, line 19. Moreover, contrary to the Examiner's indication that the specification does not teach how to use variant polypeptides of SEQ ID NO:2 having any

activity, Applicants invite the Examiner's attention to the specification at page 4, lines 27-30 or page 10, lines 21-32. For example, the claimed variants could be used for modulating the activity p38 or administered for treatment of a disorder associated with the p38 cascade.

With respect to claim 25, the Applicants further submit that claim 25 further recites that the isolated DNA molecule encode a constitutively active polypeptide. In view of the teachings of the specification at page 6, line 25 to page 7, line 2 and standard mutagenesis techniques known in the art, the DNA molecules claimed in claim 25 are clearly enabled. One skilled in the art would be able to make modifications using standard techniques and assay the molecules for constitutive activity using assays for MEK6 canasta activity described in the specification. Applicants also invite the Examiner's attention to page 7, lines 9-11 of the specification which provides that constitutively active polypeptide variants as claimed in claim 25 would be useful in gene replacement therapy for patients.

One skilled in the art would not require ingenuity to practice the claimed invention given the teachings of the specification. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 U.S.P.Q. 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd. sub nom.*, *Massachusettts Institute of Technology v. A.B. Fortia* 774 F.2d 1104,227 USPQ 428 (Fed. Cir. 1995). In view of the foregoing, Applicants submit that the rejection of the claims under 35 U.S.C. § 112, first paragraph should be withdrawn.

The Rejections Under 35 U.S.C. § 112, Second Paragraph Should Be Withdrawn

The Examiner has maintained the rejection of claims 25-26 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner objects to claims 25-26 in that claim 25 recites the phrase "constitutively active" and claim 26

recites the phrase "constitutively inactive." As noted previously, claim 26 has been canceled without prejudice, thereby rendering the Examiner's rejection of the claim moot.

Contrary to the Examiner's position, Applicants respectfully submit that the one skilled in the art would understand the scope of the phrase "constitutively active." The Examiner acknowledges that the specification does contain a definition of "constitutively active" at page 6, lines 31-34; however, the Examiner maintains that the definition is not a definite definition but offers examples or preferred meanings. The Examiner concludes that the claims are rendered indefinite because the claims could refer to many polypeptides with many different activities and that the scope of the polypeptides claimed is unclear. Applicants submit that the definition is definite. "Constitutively active" polypeptides display the ability to stimulate p38 phosphorylation in the absence of stimulation by cytokines, UV, stress-inducing agents or osmotic shock. The ability to stimulate p38 phosphorylation in the absence of certain stimulants is a specific activity that makes the scope of the claimed polypeptides clear. As discussed in the MPEP at 2173.01 and case law, it is a fundamental principle that Applicants are their own lexicographers. As long as the terms are not used in ways that are contrary to accepted meanings in the art, Applicants can use any type of language to define claimed subject matter. *In re Swinehart*, 439 F.2d 210, 160 USPQ 226 (CCPA 1971). Applicants submit that the definition of "constitutively active" satisfies the statutory requirement as the specification states the meaning that the term is meant to have. One of skill in the art would be apprized of the scope of the invention read in light of the specification. In view of the foregoing, Applicants submit that the scope of claim 25 is clear to one skilled in the art and request that the rejection of pending claim 25 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn.

Double Patenting

The rejection of claims 23-26 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 6,074,862 has been maintained. Applicants request that this rejection be held in abeyance until such time as allowable subject matter is indicated.

CONCLUSION

Applicants respectfully request that the amendments and remarks of the present response be entered and made of record in the instant application, and that the Examiner reconsider the rejections in view of these amendments and remarks. Accordingly, after entry of this Amendment, all of the pending claims should be in condition for allowance. Withdrawal of the rejections and allowance of all the claims is earnestly requested.

Applicants respectfully request that the Examiner call Anthony M. Insogna at (212) 790-9090 if any questions or issues remain.

Respectfully submitted,

Date November 4, 2002

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Enclosure

APPENDIX A

Marked Version of the Specification Replacement Paragraph

U.S. Patent Application Serial No. 09/593,288

Attorney Docket No. 10624-021-999

On page 3, the paragraph beginning "Figure 1":

Figure 1 presents the nucleotide (SEQ ID NO:1) and primary amino acid (SEQ ID NO: 2) sequence of MEK6, as deduced from the sequence of cDNA clones isolated from a human MOLT-4 cDNA library. For the amino acid sequence, standard one-letter codes are utilized.

APPENDIX C

Marked-Up Copy of the Amended Claim

U.S. Patent Application Serial No. 09/593,288

Attorney Docket No. 10624-021-999

23. An isolated polypeptide comprising a variant of the amino acid sequence provided in SEQ ID NO:2 that differs from SEQ ID NO:2 than 10% of the amino acid residues, wherein said polypeptide is capable of phosphorylation of a substrate.